

Balancing the outcomes: reporting adverse events

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When decisions about a new intervention are being made, the “net clinical benefit” of the intervention needs to be assessed. This requires balancing all the reported benefits and side effects of the intervention. The adverse events experienced in a trial must be known in sufficient detail for their severity and relationship to treatment allocation to be judged. Reporting of such events is the subject of item 19 of the CONSORT statement (Box 1).¹

What is an adverse event?

The definition of adverse events (AEs) adopted by the International Conference on Harmonization (ICH) is shown in Box 2; it is designed to document all untoward events occurring in a clinical trial.^{2,3} AEs are thus both those events for which there is a known or plausible association with treatment and those for which there is none. Adverse drug reactions (ADRs) are those AEs that may reasonably be attributed to the medication (Box 2), distinguishing between medications that are used in accordance with their marketing approval (eg, in the approved dose, patient population and indication) or not.^{2,3} AEs are also classified as being serious or non-serious (Box 2 and Box 3).

Standard schemes used to classify AEs, usually by body system, allow for easier comparison between different trial results and between different treatment options. Examples include the *International classification of diseases*,⁴ and the *Medical dictionary for regulatory activities*.⁵ Some classifications also grade severity of AEs, such as the *Common terminology criteria for adverse events* (CTCAE) system of the United States National Cancer Institute,⁶ which has five grades of severity, ranging from 1 (mild) to 5 (death).

Regulatory requirements for reporting adverse events

To reliably report on AEs, procedures must be in place from the beginning of a trial for systematically recording and reporting them.² All investigators participating in a clinical study, and their respective human research ethics committees (HRECs), must have been provided with an investigator's brochure which includes all relevant information known about the safety, efficacy and pharmacodynamics of the investigational drug, and a description of the possible risks and adverse drug reactions associated with the drug and similar products.²

Good clinical practice guidelines require investigators to report immediately to the trial sponsor any serious AEs that occur during the conduct of a trial.² In turn, many countries require the study sponsor to then report these to national regulatory authorities. An

1 CONSORT checklist of items to report when reporting a randomised trial¹

Section and topic	Item no.	Descriptor
Results		
Adverse events	19	All important adverse events or side effects in each intervention group.

AE which is considered to be a serious unexpected adverse drug reaction⁷ must be notified by the sponsor to relevant regulatory authorities as an “expedited” SAE within 7 days of awareness for events that were fatal or life-threatening, and within 15 days for others.³ ICH guidelines for good clinical practice, as adopted internationally, also specify that all serious unexpected adverse drug reactions should be reported to the relevant HRECs.⁷

2 Definitions adopted by the International Conference on Harmonization, and adopted by Australia's Therapeutic Goods Administration²

Adverse event

An *adverse event* is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medical (investigational) product.

Adverse drug reaction

Before marketing approval: all noxious and unintended responses to a medicinal product related to any dose should be considered *adverse drug reactions*. The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

After marketing approval: a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Unexpected drug reaction

An adverse drug reaction, the nature or severity of which is not consistent with the applicable product information (eg, investigators' brochure for an unapproved investigational medication).

Serious adverse event or reaction

Any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Causes a congenital anomaly or birth defect

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It is not possible to assess the significance of AEs from reports in which the treatment allocation remains blinded and the number of participants exposed to the trial medications is unknown. Hence, Data and Safety Monitoring Boards (with the ability to review events and their frequencies unblinded, if preferred) are an important (although insufficiently used⁸) mechanism for protecting the safety of trial participants⁹ and for ensuring that studies are stopped as soon as it becomes clear that the trial intervention is beneficial or harmful.^{10,11}

Australian requirements for adverse event reporting

In Australia, the Therapeutic Goods Administration (TGA) only requires reports on serious unexpected adverse drug reactions that occur *in Australia*, and that it be informed of any significant safety concerns that arise from the sponsor's monitoring of overseas safety reports and of any action undertaken by overseas regulatory agencies.³ In Australia, the section of the ICH good clinical practice guidelines on reporting to HRECs has been overridden by the *National statement on ethical conduct in research involving humans*.¹² This mandates that investigators inform the TGA and HRECs of "all serious or unexpected AEs that occur during the trial and may affect the conduct of the trial or the safety of the participants or their willingness to continue participation in the trial". One consequence of this directive is that HRECs in Australia are being inundated with large numbers of essentially uninformative AE reports.⁸

Presentation of adverse event reports

Patient selection can influence the rates of AEs. It is important that the trial population is described adequately so that clinicians can assess the risk of a particular treatment for an individual patient. It is also important that the mechanisms used to elicit reporting of AEs are documented. Volunteered reports of AEs can give incidences of AE markedly different from those ascertained through checklists or diaries.^{13,14}

Counts of adverse events

The numbers of patients who had each type of AE should be clearly detailed in the study report. If some patients experience more than one type of AE, the numbers of each event type should also be documented.¹ Both the number of patients experiencing at least one occurrence of the event of interest (for statistical analyses) and the total number of such events observed (for cost-benefit analysis) help interpretation (Box 4).

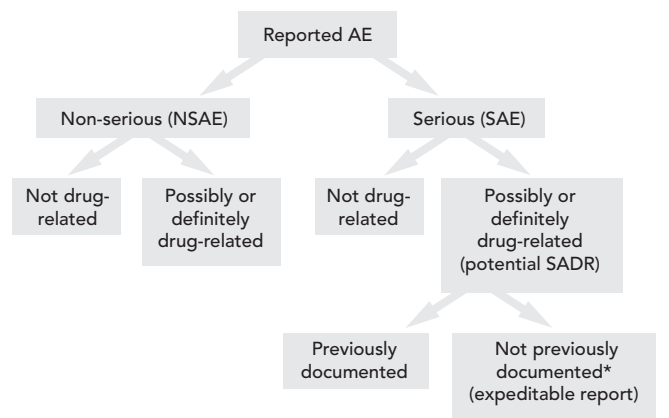
Types of adverse events

The types of events chosen for reporting must be prespecified and may be selected on the basis of absolute numbers of events (ie, the most common events), biological relevance to the drug or study question, clinical relevance, or safety (ie, serious or severe events are reported).

Adverse events by treatment

Presentation and comparisons of AEs are generally reported by allocated treatment (ie, the intention-to-treat [ITT] principle), but reporting by "treatment actually received" can also be useful in some settings. For example, where non-compliance rates with allocated treatment are substantial, ITT analyses will under-report treatment-related AEs. However, analyses by "treatment actually

3 Severity and causality of adverse events (AEs)



* Or more severe than previously known.

NSAE = non-serious adverse event; SAE = serious adverse event; SADR = serious adverse drug reaction.

received" will provide only non-randomised comparisons and therefore contain a varying degree of selection bias.¹⁶ Therefore, ITT methods should be routinely reported, and data for treatment actually received should be added, with an explanation as to why, if there are high rates of non-compliance.

Treatment withdrawal after adverse events

Adverse events resulting in withdrawals from treatment should also be adequately described, as they reflect tolerability of treatment, and will be useful for both patients and clinicians to better assess the importance of particular reported AEs.

Abstracts and keywords

Finally, when the study is published, the abstract and keywords should mention the term "adverse events", even if none occurred in the study, to facilitate retrieval of AE data from databases such as MEDLINE.¹⁷

4 Checklist for presenting adverse event (AE) reports

- Describe methods used to ascertain AEs (eg, reported by physician or patient)
- Show events which are unexpected in the context of the treatment given
- Categorise the seriousness of events where relevant
- Report AEs by the number of patients affected and by the number of events
- Report AEs by intention-to-treat methods (may additionally be shown by treatment actually received)
- Highlight AEs whose severity causes withdrawal or modification of treatment
- Highlight substantial differences in the risk of an AE for different subgroups of participants
- Use time-to-event (Kaplan-Meier survival) methods to avoid inflated estimates, where discontinuation rates have been high in long-term trials¹⁵
- Mention key AE findings in the abstract and keywords of the report

5 Numbers of patients that need to be exposed to a medication to ensure that an adverse drug reaction has a 95% probability of being observed at least once

Frequency of adverse drug reaction	Minimum no. of patients required*
Very common ($\geq 10\%$)	29
Common ($1\% - < 10\%$)	299
Uncommon ($0.1\% - < 1\%$)	2994
Rare ($0.01\% - < 0.1\%$)	29956

* Number is based on the lower boundary of each category of frequency.

Current deficiencies in trial reports

A statement in the results section of a publication that “no adverse events were observed on the trial medication” without details in the methods section of the steps taken to ascertain AEs is difficult to interpret. What is less apparent is how difficult it really is to convey useful information on the types, severity and incidences of the AEs observed. Even large, multicentre studies published in first-rate journals can fail to report the number of patients who withdrew because of side effects of the trial medication. For example, a large study on the efficacy of irbesartan in preventing the development of nephropathy in patients with type 2 diabetes and microalbuminuria has the following description of the AEs observed:

“Serious adverse events during treatment and up to two weeks after treatment were recorded in 22.8 percent of the patients in the placebo group and 15.4 percent of those in the combined irbesartan groups ($P=0.02$). Nonfatal cardiovascular events were slightly more frequent in the placebo group (8.7 percent, vs. 4.5 percent in the 300 mg group; $P=0.11$). The study medication was permanently discontinued in 18.9 percent of the patients in the placebo group, as compared with 14.9 percent of those in the combined irbesartan groups ($P=0.21$).”¹⁸

In the report, the AEs that led to discontinuation were not described. Furthermore, it was unclear whether they were related to the condition being treated, to the trial medication, or to intercurrent illnesses.

Guidelines have been developed to help researchers give useful information about AEs for reporting, both in general¹ and for particular classes of trial, such as chemotherapy¹⁹ or postoperative analgesia.¹³ The need for such guidelines is evident from studies of adequacy of AE reporting. In one evaluation of reporting of safety data from clinical trials of HIV treatment, the severity of AEs was regarded as adequately defined in only a third of trials.²⁰ In a subsequent study in other clinical areas, only 39% of trials adequately reported clinical adverse effects and only 29% adequately reported laboratory-determined toxicity.²¹ Other studies show similar rates of deficiencies in AE reporting in a variety of circumstances.²²⁻²⁵ These deficiencies are serious, as they can prevent clinicians from being able to provide patients with balanced information about the scale and scope of risks associated with different treatment strategies.

Even when AEs have been well described, retrieving data about them can be problematic — of a sample of 37 trials indexed on MEDLINE or EMBASE known to present AE data, only 49% could be found by searching for text words such as “adverse event”, “side

effect” or “h(a)emorrhage”, while adding indexing terms relevant to AEs only improved retrieval to 78%.¹⁷

Conclusion

Large randomised controlled trials and meta-analyses of randomised controlled trials are very effective in distinguishing AEs that are caused by the underlying condition from those that are related to the intervention. They can provide clinicians with unbiased information about the frequency and severity of adverse effects at a time when a drug or procedure is new. While other mechanisms for obtaining safety data are needed to detect AEs that are too rare to be detected by even the largest studies (Box 5), or that occur in groups of patients who would normally be excluded from trials (eg, because of illness severity, comorbid conditions or the need for potentially confounding therapies), these do not allow clinicians to quantify the risk of a treatment²⁶ and can give markedly different impressions of the incidence of adverse drug reactions compared with those obtained from randomised clinical trials.²⁷ Only proper reporting of AEs from randomised controlled trials allows adequate assessment of the potential net clinical benefits of interventions.

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Competing interests

None identified.

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